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Effectiveness and safety of bortezomib-dexamethasone regimen in patients with multiple myeloma: A prospective observational study

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ABSTRACT

Background: Bortezomib and dexamethasone (BD) regimen offers a promising therapeutic approach in multiple myeloma (MM) by inhibiting the proteolytic pathway of tumor cells. **Aims and Objectives:** This study aims to assess the safety profile and treatment outcomes of MM patients undergoing the BD regimen. **Materials and Methods:** This prospective observational study included MM patients who received BD regimen. Patients received bortezomib (1.3 mg/m^2 intravenous) weekly for 4 weeks along with dexamethasone (40 mg orally) weekly for 4 weeks. Clinical assessments were performed after each cycle, and adverse drug reactions were graded according to National Cancer Institute criteria. Treatment outcomes were evaluated after the 4th cycle based on specific parameters. **Results:** Thirty-seven patients, with a mean age of 56.2 years, predominantly male (56.8%), were included. Common symptoms included bone pain, fatigue, weight loss, and appetite loss. Toxicities were mainly grade 1 and 2, with peripheral neuropathy (PN) being the most prevalent. The BD regimen exhibited a response rate of 65%, accompanied by significant improvements in bone marrow plasma cells, β2 microglobulin, immunoglobulin assay, and erythrocyte sedimentation rate. In addition, treatment improved performance status, in 51.4% of patients achieving scores above 90 on the Karnofsky scale. **Conclusion:** The BD regimen demonstrated notable efficacy and tolerability in MM treatment. However, it is associated with a higher risk of PN.

Key words: Plasma cell neoplasm; Proteosome inhibitor; Performance status; Peripheral neuropathy; Karnofsky scale

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INTRODUCTION

Multiple myeloma (MM) is a hematological malignancy characterized by the clonal proliferation of plasma cells in the bone marrow, leading to the production of monoclonal immunoglobulins. It is the most prevalent malignant plasma cell disorder globally and the second most common hematological malignancy.[1] Approximately 10% of all hematologic malignancies are attributed to MM.[2] In 2020, the National Cancer Registry reported a projected number of 18,481 cases of MM in India, corresponding to a cumulative risk of 1.3 cases per 100,000 population.[3]

Bortezomib, a proteasome inhibitor, has revolutionized the treatment landscape for MM. By disrupting the proteolytic pathway within tumor cells, bortezomib exerts potent anti-myeloma effects, leading to apoptosis and inhibition of cell proliferation.[4] The efficacy of bortezomib has been already proven as both as a single agent and in combination with other drugs such as dexamethasone, lenalidomide, or

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thalidomide, in inducing responses and improving survival outcomes in MM patients.[5-7]

While clinical trials offer valuable insights into the efficacy and safety of bortezomib-based regimens, observational studies and retrospective analyses have emphasized the tolerability profile of bortezomib and its impact on treatment outcomes in diverse patient populations.[8-12] There is still a dearth of evidence from Indian population on MM patients undergoing bortezomib-based therapies.[13-15] With this background, this study was conducted to elucidate the effectiveness and safety profile of bortezomib-based regimens and to determine the quality of life of MM patients in South India.

Aims and objectives

Primary: To determine the safety profile of bortezomib in multiple myeloma patients.

Secondary: To determine the effectiveness of bortezomib in multiple myeloma patients.

To estimate the quality of life of patients using the Karnofsky performance status scale in multiple myeloma patients.

MATERIALS AND METHODS

The study was designed as a prospective observational study and conducted in the Department of Radiotherapy at a tertiary care teaching hospital after obtaining institutional ethics committee clearance (Letter No: IEC No.01/24/2015/MCT Dated January 24, 2015). The study period spanned 1½ years, from February 2015 to August 2016.

The study population comprised patients diagnosed with MM who were undergoing BD chemotherapy regimen. Inclusion criteria encompassed patients above 18 years of age, regardless of gender, willing to provide informed written consent, capable of speaking English or Malayalam, and newly diagnosed with MM meeting specific criteria related to bone marrow plasma cells, measurable disease, lytic bone lesions, serum monoclonal protein level, hemoglobin level, and platelet count. Exclusion criteria included unwillingness to participate or provide relevant information, pregnancy or lactation, pre-existing motor or sensory neuropathy, and uncontrolled infections or cardiovascular disease.

Patients were administered bortezomib 1.3 mg/m^2 intravenously weekly for 4 weeks, along with dexamethasone 40 mg orally weekly for 4 weeks, with a 2-week gap between cycles. History, examination, and baseline investigations were recorded before treatment initiation. Subsequent assessments were conducted after the 2nd, 4th, and 6th cycles of chemotherapy, evaluating treatment response, toxicity symptoms, and performance status.

Outcome assessment after the 4th cycle was based on parameters including β2 microglobulin, Ig assay, erythrocyte sedimentation rate (ESR), and bone marrow plasma cells. Treatment continuation or alternative therapy adoption was determined based on treatment effectiveness. Performance status was assessed using the Karnofsky performance status scale.

Beta 2 microglobulin, a low-molecular-weight protein on the surface of all nucleated cells, serves as the light chain of the human leukocyte antigen histocompatibility complex. Levels >3 mcg/mL are considered a poor prognostic factor, while levels below 3 mcg/mL post-treatment indicate a good response to therapy.

The body produces five types of immunoglobulins: IgG, IgM, IgA, IgE, and IgD. In myeloma cases, IgG accounts for 60–70% and IgA for about 20%. A good response to treatment is indicated by the return of the respective immunoglobulin to normal values.

Similarly, An ESR drop to <20 mm/h indicates complete remission, while values above 20 mm/h suggest partial remission or treatment failure. A high number of plasma cells in the bone marrow is also a key diagnostic feature of MM. A decrease to <5% indicates complete remission, 5–10% indicates partial remission, and more than 10% indicates treatment failure.

The Karnofsky Performance Status Scale is a widely used tool in medical practice for assessing the functional status and overall well-being of patients, particularly those undergoing cancer treatment.[16] Developed by Karnofsky, this scale assigns a numerical score ranging from 100 to 0, with 100 representing "perfect" health and 0 indicating death. The scale evaluates a patient's ability to perform daily activities and tolerate medical interventions, providing valuable insights into their quality of life and prognosis. Higher scores indicate better functional capacity and greater ability to withstand aggressive treatments, while lower scores may signal deterioration in health and decreased tolerance to medical interventions.

During patient visits, any toxicity symptoms were carefully observed and documented, and an evaluation of toxicity was conducted following the National Cancer Institute (NCI) toxicity criteria, specifically using common terminology criteria for adverse events (CTCAE) version 4.[17] The highest toxicity experienced by a patient during any cycle was regarded as their overall toxicity grade.

CTCAE version 4 provides a comprehensive framework for categorizing and quantifying treatment-related toxicities based on their clinical manifestations and impact on patient well-being. This system assigns grades ranging from 1 to 5 to denote the severity of adverse events, with Grade 1 indicating mild symptoms and Grade 5 representing life-threatening complications or death.

Statistical analysis

The sample size for this study was calculated using the formula, $N = (Z^2 \times P \times Q)/d^2$ where N represents the sample size, Z is the Z value corresponding to the desired level of confidence (1.96 for a 95% confidence level), P is the proportion of people suffering from toxicity (75%), Q is the complement of P, and d is the margin of error.[18] With these parameters, a minimum sample size of approximately 33 participants was determined.

The data were inputted into Microsoft Excel 2013 and subsequently analyzed using the Statistical Package for the Social Sciences version 21. Quantitative variables were represented by their mean and standard deviation, while qualitative variables were presented as frequency distributions. The comparison of qualitative variables between pre-test and post-test stages was evaluated using the McNemar's test, with a significance level set at a P=0.05.

RESULTS

A prospective evaluation was conducted on 37 patients receiving the bortezomib and dexamethasone (BD) regimen for MM at the Department of Radiotherapy, Government Medical College Hospital, Thiruvananthapuram, from February 2015 to August 2016. Although the calculated sample size was 33, the study included 37 patients to ensure a more robust data analysis.

Baseline demographics

The study population had an age range of 42–68 years, with a mean age of 56.2±7.5 years. The youngest age group (40–44 years) included 5% (2) patients, while the highest number of cases 24.3% (9) was in the 55–59-year age group. In terms of gender distribution, of the 37 patients observed, 16 were female (43.2%) and 21 were male (56.8%).

Clinical presentation

The clinical presentation data revealed that bone pain was the most prevalent symptom, affecting 59.5% (22) of patients, followed by loss of appetite, loss of weight, and pallor, each observed in 48.6% (18) of individuals. Fatigue was also common, affecting 45.9% (17) of the study population. Abdominal symptoms were reported in 18.9% (7) of cases, while fever was present in 10.8% (4) of patients. Very few had edema (5.4%), oliguria (2.7%), and cough (2.7%).

Safety profile

The adverse drug reaction (ADR) profile was assessed during the 2nd, 4th, and 6th cycles of chemotherapy, with the highest grade of toxicity recorded for each patient. Peripheral neuropathy (PN) was the most prevalent adverse effect, affecting 35.14% (13) of patients, followed by anemia in 19% (7) of individuals.

Approximately 43.24% of patients experienced gastrointestinal side effects, with vomiting being the most prevalent at 16.21% (6), followed by diarrhea at 10.8% (4). Nausea and constipation affected 8.1% (3) of cases each, while fatigue was observed in 5.4% (2) of patients. Anorexia was reported in all 37 patients (100%). Among those experiencing nausea (8.1%), 66.7% had Grade 1 and 33.3% had Grade 2. Vomiting was predominantly Grade 1 (83.3%) and Grade 2 (16.7%) among the 16.21% affected patients. Constipation affected 8.1% of patients, all of whom experienced Grade 1. Diarrhea was reported in 10.81% of patients, all experiencing Grade 1.

Neurological toxicity primarily manifested as PN, observed in 35.1% (13 patients) of individuals receiving the BD regimen. Among those affected, 53.8% (7 patients) experienced Grade 1 PN, while 46.2% (6 patients) had Grade 2 PN. Fatigue was also prevalent, noted in 5.4% (2) of the patients. Out of the two patients, one had Grade 1, while the other had Grade 2 fatigue. Other minor ADRs observed with the BD regimen included dizziness, reported in 2.7% (1 patient), and herpetic skin lesions, noted in 5.4% (2 patients) of the study population. Throughout the study period, there was mortality reported.

Effectiveness measures

The effectiveness was evaluated across four key criteria: bone marrow plasma cells, β2 microglobulin levels, immunoglobulin value, and ESR. 65% (24) patients treated showed a positive response based on criteria such as bone marrow plasma cells, β2 microglobulin, immunoglobulin value, and ESR, while the remaining 35% (13) did not respond favorably and were subsequently switched to other treatment options.

β2 microglobulin

At diagnosis, only 4 patients (10.8%) had β2 microglobulin levels below 3 mcg/mL, while the remaining 33 patients (89.2%) had levels exceeding this threshold. Following treatment, 23 patients (62.2%) achieved β2 microglobulin levels below 3 mcg/mL. Among the initial 33 patients with β2 microglobulin >3 mcg/mL, 19 (57.6%) attained levels below 3 mcg/mL post-treatment, while 14 (42.4%)

Table 1: Change in β2 microglobulin values after treatment

β2 Microglobulin (mcg/mL)	After treatment		Total (n)	P-value
	<3	>3		
Before treatment				
<3	4	0	4	P<0.001
>3	19	14	33	
Total	23	14	37	

retained high levels despite therapy, indicating a statistically significant difference (P<0.001) (Table 1).

Immunoglobulin levels

Before therapy, 24 patients (64.9%) had high immunoglobulin values, while 13 patients (35.1%) had normal values, as shown in Table 2. After treatment, 14 out of these 24 patients (58.3%) shifted to normal values, while the remaining 10 patients (41.7%) still exhibited high levels. This change was statistically significant (P<0.001) (Table 2).

ESR

At diagnosis, most patients had elevated ESR values. Thirty-five patients (94.6%) initially had high ESR values. Post-treatment, ESR normalized in 25 of these patients (71.4%), while 10 patients (28.6%) continued to have high ESR levels. This reduction was statistically significant (P<0.001) (Table 3).

Bone marrow plasma cells

At diagnosis, nearly all patients had bone marrow plasma cells exceeding 5%;16.2% (6) patients had plasma cells between 5% and 10%, while 83.8% (31) had levels above 10%. Following BD treatment, 14 patients (37.8%) achieved a complete remission with plasma cell counts dropping below 5%, 10 patients (27%) reached partial remission with counts between 5% and 10%, and 13 patients (35.1%) continued to have more than 10% plasma cells. Among the initial 6 patients with 5-10% plasma cells, 5 saw a reduction to below 5%, and only 1 remained in the 5–10% range. Of the 31 patients with more than 10% plasma cells, post-treatment counts fell below 5% in 9 patients, decreased to 5–10% in another 9, and remained high in the remaining 13. This reduction was statistically significant (P<0.001) (Table 4).

Performance status of patients

In this study, the performance status before treatment predominantly fell between 60 and 80. The improvement in performance status after treatment was statistically significant (P<0.001). This indicates that the treatment had a substantial positive impact on the patients' quality of life and their ability to withstand chemotherapy (Table 5).

Table 2: Change in immunoglobulin value after treatment

Ig	After treatment		Total	P-value
	High	Normal		
Before treatment				
High	10	14	24	P<0.001
Normal	0	13	13	
Total	10	27	37	

Table 3: Change in ESR values after treatment

ESR	After treatment		Total	P-value
	<20	>20		
Before treatment				
<20	2	0	2	P<0.001
>20	25	10	35	
Total	27	10	37	

Table 4: Change in bone marrow plasma cells after treatment

Bone marrow plasma cells	After treatment			Total	P-value
	<5	5-10	>10		
Before treatment					
<5	0	0	0	0	P<0.001
5–10	5	1	0	6	
>10	9	9	13	31	
Total	14	10	13	37	

Table 5: Performance status of the patients

Performance score	Before treatment (%)	After treatment (%)	P-value
60	15 (40.5)	0	P < 0.001
70	12 (32.4)	2 (5.4)	
80	10 (27)	16 (43.2)	
90	0	19 (51.4)	
Total patients	37	37	

DISCUSSION

This prospective observational study aimed to determine the toxicity profile, outcome, and performance status of patients receiving the BD regimen for MM. The age range of the study population was 42–68 years, with a mean age of 56.2 years. These demographics are consistent with studies by Harousseau et al.,[19] and Yuan et al.,[20] where the mean ages were 55–56 years, respectively. The majority of the patients were in the 55–59 year age group, with a male predominance (56.8%).

Bone pain was the most common symptom, observed in 59.5% of patients, similar to findings by Kyle et al., where bone pain was seen in 58% of patients.[21] Other symptoms included loss of weight, loss of appetite, and fatigue, which were also prevalent.

The toxicity profile of the BD regimen, as assessed and graded according to the NCI toxicity criteria version 4, revealed gastrointestinal and hematological adverse effects, as well as PN and herpetic skin lesions. The incidence of these toxicities was generally consistent with previous studies, with some variations in specific adverse effects such as diarrhea and anemia. Gastrointestinal side effects were seen in 43.2% of patients, which is consistent with the 48% reported by Harousseau et al.[19] Among gastrointestinal adverse effects, anorexia was present in all patients but was mild (Grade 1). Nausea, vomiting, constipation, and diarrhea were also reported, with most cases being Grade 1 or 2. The incidence of diarrhea in this study (10.8%) was lower than the 18% reported by Yuan.[20]

Hematological toxicity was primarily anemia, seen in 19% of patients, mostly in Grade 1 and Grade 2 categories, with only one case of Grade 3 toxicity. This finding aligns with Harousseau et al., where anemia was also a common hematological toxicity.[19]

PN was the most common neurological toxicity, affecting 35.1% of patients, with 54% experiencing Grade 1 and 46% experiencing Grade 2 neuropathy. This is in line with the study by Harousseau et al., where PN was seen in 30% of patients.[19] The herpetic skin lesions were noted in 5.4% of patients, consistent with Harousseau et al.[19] These findings underscore the importance of monitoring and managing these toxicities to ensure the well-being of patients undergoing the BD regimen.

Out of 37 patients treated with the BD regimen, 29 (78%) showed positive outcomes, with all parameters (β2 microglobulin levels, immunoglobulin values, ESR, bone marrow plasma cell counts) showing statistically significant improvements. These findings align with studies by Harousseau et al.,[19] Jagannath et al., (CREST study),[22] Dimopoulos et al.,[23] and Chen et al.,[24] which reported identical response rates of 62–66%. Hence, the BD regimen effectively reduces tumor burden and systemic inflammation, supporting its use in MM treatment.

Similarly, CASTOR trial found that the BD regimen, combined with daratumumab (D-Vd), led to substantial improvements in patients' performance status, quality of life, and clinical response rates.[25] Improvements were statistically significant, indicating a robust treatment effect which is consistent with our findings.

Limitations of the study

This prospective observational study evaluating the BD regimen in MM is limited by its small sample size of 37 patients, short follow-up period, and single-center design, which reduce the generalizability and long-term applicability of the findings. The absence of a control group and the subjective nature of performance status improvements introduce potential biases, further limit the study's conclusions.

CONCLUSION

The BD regimen demonstrates significant effectiveness in treating MM, with a substantial portion of patients showing positive outcomes across various clinical parameters. Improvements in β2 microglobulin levels, immunoglobulin values, ESR, and bone marrow plasma cell counts indicate the regimen's ability to effectively control disease progression and enhance patient quality of life. This study underscores its potential as a valuable treatment option for MM, warranting its continued use in clinical practice.

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NN- Definition of intellectual content, literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation, and submission of article**; SK-** Manuscript preparation, editing, and manuscript revision; **MKD-** Review manuscript**; JJ-** Literature survey, coordination, and manuscript revision.

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